Remarks/arguments

Claims 1-10, 12-19, and 24-54 are pending. Claims 27-40 and 50-54 have been withdrawn. Claim 1 has been amended to correct a typographical error.

Terminal Disclaimer

The previously submitted terminal disclaimer was not entered because the Examiner contends that it did not comply with 37 CFR 1.321 (b) and/or (c). A compliant terminal disclaimer has been submitted with this paper.

Claim Objection

Claim 1 has been objected to because "naloxonazine" is misspelled. This objection should be withdrawn because the spelling has been corrected by amendment.

Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 1-10, 12-19, 24-26, and 41-49 have been rejected for failure to comply with the written description requirement. According to the Examiner, the specification does not describe a plurality of formulations.

Applicants respectfully traverse this rejection. Paragraph 46 of the instant specification defines the claim terms "invariate" and "independent," which relate to release of the active agents. "[I]ndependent release ... applies to formulations that have different amounts of the active compounds but are otherwise identical or at least highly similar with respect to the components that essentially influence the release behaviour." "[I]nvariate release ... is defined so that the percentage of the absolute amount of each active compound released per time unit does not significantly change and remains sufficiently constant ... if absolute amounts are changed." Thus, both terms describe a plurality of formulations, i.e., formulations with different amounts of the active compounds. Accordingly, this rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-10, 12-19, 24-26, and 41-49 have been rejected under 35 U.S.C. § 112, second paragraph because the Examiner contends that the phrase "a plurality of storage stable pharmaceutical formulations" is not clear. The Examiner states that: "[t]his recitation appears to require a collection of compositions, but it is not clear if this requires a single preparation that is

composed of a set of formulations that may or may not be composed of [the] same components or it the recitation is simply a genus of formulations." Office Action., p. 4. The Examiner interpreted the phrase to mean a genus of formulations in applying the prior art. *Id.*

The Examiner correctly interpreted the phrase "a plurality of storage stable pharmaceutical formulations" to refer to a genus of formulations.. The genus comprises formulations which release the active compounds in a sustained, invariant and independent manner. Applicants request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

1. Claims 1-10, 12-19, 24-26, and 41-49 have been rejected under 35 U.S.C. § 103(a) as obvious over EP 0699436 (Miller), in view of U.S. Patent No. 4,457,933 (Gordon) and U.S. Patent No. 6,306,438 (Oshlack).

According to the Examiner, Miller teaches an oral, sustained release composition that releases the hydrochloride salt of tramadol and, more specifically, an uncoated tablet with tramadol hydrochloride, ethyl cellulose, lactose, cetosteraryl alcohol, magnesium stearate, and talc. Further, the composition can contain at least one long chain hydrocarbon, which includes stearic acid. Office Action, p. 6. The Examiner acknowledges that Miller does not teach including an opioid antagonist, nor stability over a two year period.

According to the Examiner, Gordon teaches the combination of an opioid analgesic and antagonist in an oral composition in a ratio of 3.5:1, where the antagonist, naloxone, is present at 1 to 3 mg. Further, Gordon teaches the administration of the hydrochloride salt of naloxone and oxycodone. Office Action, p. 6-7.

The Examiner states that Oshlack teaches a composition similar to that in Miller, where ethyl cellulose is combined with stearyl alcohol and tramadol hydrochloride, and the conditions for storing the composition for two years.

According to the Examiner, it would have been obvious to exchange an oxycodone salt for the tramadol salt in Miller because they are functionally equivalent opioids. Further, it would have been obvious to include naloxone in the composition in the ratios and amounts taught by Gordon because opioids are prone to abuse. The Examiner also states that the limitations that the matrix is a diffusion matrix that is substantially non-erosive, substantially non-swellable that

releases the compounds in an invariant and independent manner are properties of the composition based upon its constituent materials. Office Action, p. 7-8.

Applicants respectfully traverse this rejection. The following arguments are supported by the Declaration under 37 C.F.R. 1.132 of Christian Leuner, attached hereto ("the Declaration"). Dr. Leuner is the Functional Director of Analytical and Pharmaceutical Sciences at Mundipharma Research GmbH & Co. Mundipharma GmbH & Co is a company associated with the instant assignee, Euro-Celtique S.A. A copy of Dr. Leuner's *curriculum vitae* is attached as an exhibit to the Declaration.

Applicants note that, contrary to the Examiner's assertion, Gordon does not teach a sustained release oral opioid composition in its general or specific disclosure. For example, the excipients recited in column 1, lines 5-21 of Gordon do not provide sustained release. Declaration at 14. Gordon teaches an immediate release oxycodone and naloxone composition. Gordon does not disclose or suggest any substantially non-swellable diffusion matrix, much less that such a matrix releases active compounds in a sustained, invariant and independent manner.

The instant claims are directed to a plurality of formulations wherein the active compounds are released from a substantially non-swellable diffusion matrix of each formulation in a sustained, invariant and independent manner. The instant specification states that "'independent release' means that, given the presence of two active compounds, a change in the absolute amount of one compound does not influence the release profiles of the other compounds so that the release profiles of the other compounds are not changed" (specification, para. 42), and "invariant release profile" means that "the percentage of the absolute amount of each active compound released per time unit does not significantly change and remains sufficiently constant (and does not substantially change) if absolute amounts are changed" (specification, para. 46). See, *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) ("[T]he specification is always highly relevant to the claim construction analysis."). According to the specification, "independent" and "invariant" preparations can "differ with respect to the amount of the active compounds, but are of the same or at least highly similar composition with respect to the release-influencing components of the preparation. Typically, the difference in the amount of an active compound will be replaced by the amount of a pharmaceutical inert excipient which does not substantially influence the release behaviour of the preparation." Specification, para. 48.

The invariant and independent release of active compounds according to the present invention is an important clinical feature because it allows for efficient dosage adaption. As the release for each active compound will be the same at the different amounts, a physician can be sure that the beneficial characteristics of the combination of active compounds can be achieved across the whole dosage range. The benefits of independent and invariate release include, not only prevention of e.g. oral abuse, but also effective treatment of side effects such as constipation.

One of ordinary skill in the art at the time the instant application was filed would have understood that the release profile of an agent (or compound), whether active or inert, from a matrix depends upon the physical chemistry properties of the agent in relation to the release-influencing components and other agents within the formulation, and not the functional properties of the agents. Declaration at 20. Such physical chemistry properties are drug specific and include, for example, the diffusion coefficient, pK, solubility, molecular weight, hydrogen donor and acceptor sites, and the partition coefficient. *Id.* Thus, prior art which may suggest (according to the Examiner) that one of ordinary skill in the art would combine an opioid agonist and an opioid antagonist into the claimed formulations is inapplicable here. *Id.* at 21. The functional properties (i.e., opioid agonism and antagonism) of the active agents are not pertinent to whether a formulation such as instantly claimed would reasonably be expected to provide "independent" and "invariant" release. *Id.* One or ordinary skill in the art would not reasonably expect, nor predict, that combining active compounds based on their functional characteristics would result in a plurality of formulations wherein the active compounds are released in an independent and invariate manner.

In addition to release of two active agents from the matrix according to the instant invention, the inert pharmaceutical excipients may also be released. *Id.* at 22. One of ordinary skill in the art would have understood that the release of the pharmaceutically inert excipient is also dependent on its physical chemistry properties in relation to the release-influencing components, the active agents, and any other agents within the formulation. *Id.*

Miller discloses a composition containing one active agent. One of ordinary skill in the art at the time the instant application was filed would not have reasonably predicted, nor had a reasonable expectation, that a composition according to Miller, modified in accordance with

Gordon, would provide formulations comprising two active agents having "independent" and "invariate" release. *Id.* at 23.

Oshlack is directed to compositions comprising the active agent tramadol hydrochloride. As stated by the Examiner, Oshlack teaches a composition similar to that of Miller. Office Action, p. 7. For the reasons stated above pertaining to Miller, Oshlack in combination with the other prior art references, including Miller and Gordon, does not disclose, suggest, or render predictable a plurality of formulations including two active agents wherein a substantially non-swellable diffusion matrix releases the active compounds in a sustained, invariant and independent manner. Declaration at 23a.

In accordance with the above, this rejection should be withdrawn because no combination of the references discloses or suggests a plurality of formulations comprising the claimed components, and featuring invariate and independent release. That is, no combination of the references discloses, suggests, or renders predictable a plurality of formulations comprising the claimed active compounds, wherein a change in the absolute amount of one of the active compounds does not influence the release profile of the other compound, and the percentage of the absolute amount of each active compound released per time unit does not significantly change, and remains sufficiently constant, if absolute amounts are changed.

2. Claims 1-8, 10, 12-19, 24-26, and 41-49 have been rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,958,452 (Oshlack B) in view of Gordon and U.S. Patent No. 5,681,585 (Oshlack C), U.S. Patent No. 6,207,142 (Odds), and Grimm, Drug Development and Industrial Pharmacy, 1998;24:313-24 (Grimm).

According to the Examiner, Oshlack B teaches oral sustained release opioid formulations, including ethyl cellulose, tributyl citrate, stearyl alcohol, talc, and magnesium stearate. Oshlack B does not teach an opioid antagonist or stability of the preparation. The teaching of Gordon according to the Examiner is provided above. The Examiner states that Oshlack C teaches stabilized controlled release dosage forms including ethyl cellulose-containing opioid preparations, Odds teaches that two years at standard room conditions is an acceptable duration for storage stability; and Grimm teaches the standard conditions. Office Action, p. 10-11.

Oshlack B does not disclose a formulation including more than one active agent. For the reasons stated above pertaining to the Miller reference, Oshlack B does not disclose or suggest a

plurality of formulations comprising two active compounds having "independent" and "invariate" release. Declaration at 26. One of ordinary skill in the art at the time the instant application was filed would have understood that the release profile of an agent, whether active or inert, from a matrix depends on the physical chemistry properties of the agent in relation to the release-influencing components and other agents within the formulation, and not the functional properties of the agents. Declaration at 20, 26. Such physical chemistry properties are drug specific and include, for example, the diffusion coefficient, pK, solubility, molecular weight, hydrogen donor and acceptor sites, and the partition coefficient. *Id.* Prior art which may suggest that one of ordinary skill in the art would combine an opioid agonist and an opioid antagonist into the claimed formulations is inapplicable here. *Id.* at 21, 26. The functional properties (i.e., opioid agonism and antagonism) of the active agents are not pertinent to whether a formulation such as instantly claimed would reasonably be expected to provide "independent" and "invariant" release. *Id.* One or ordinary skill in the art would not reasonably expect, nor predict, that combining active compounds based on their functional characteristics would result in a plurality of formulations wherein the active compounds are released in an independent and invariate manner.

In addition to release of two active agents from the matrix according to the instant invention, the inert pharmaceutical excipient may also be released. *Id.* at 22. One of ordinary skill in the art would have understood that the release of the pharmaceutically inert excipient is dependent on its physical chemistry properties in relation to the release-influencing components, the active agents, and any other agents within the formulation. *Id.*

Gordon discloses an immediate release oxycodone and naloxone composition. Declaration at 14. Gordon does not disclose or suggest any substantially non-swellable diffusion matrix, much less such a matrix and also releases active compounds in a sustained, invariant and independent manner.

Oshlack C discloses the use of ethylcellulose in a film coating to provide controlled release of an active agent. See, e.g., Oshlack C, col. 3, ll. 57-63; col. 4, ll. 55-65. Oshlack C does not disclose or suggest ethylcellulose in a substantially non-swellable diffusion matrix, much less ethylcellulose in a substantially non-swellable diffusion matrix that releases active compounds in a sustained, invariant and independent manner. Thus, no combination of Oshlack B, Gordon,

and Oshlack C discloses, suggests, or renders predictable a plurality of formulations comprising a substantially non-swellable diffusion matrix that releases active compounds in a sustained, invariant and independent manner.

This absence of teaching is not filled by the addition of Odds and Grimm to the combined art. Odds is directed to body and hair cleansing products comprising an antifungal (see, e.g., Odds, abstract) and is cited for the proposition that government regulatory agencies recognize two years at standard room temperature as an acceptable duration for storage stability. Grimm discloses standard international stability testing guidelines.

This rejection should be withdrawn because, in accordance with the above, one of ordinary skill in the art at the time the instant application was filed would not have reasonably predicted, nor had a reasonable expectation, that a composition according to Oshlack B, modified in accordance with Gordon, Oshlack C, Odds, and Grimm would provide formulations comprising two active agents having "independent" and "invariate" release. *Id.* at 23, 26.

3. Claims 1-5 and 9 have been rejected under 35 U.S.C. § 103(a) as obvious over Oshlack B in view of Gordon, Oshlack C, Odds, Grimm, and U.S. Patent No. 6,103,261 ("Chasin).

The Examiner states that Oshlack B, Gordon, Oshlack C, Odds, and Grimm do not disclose dibutyl sebacate. Office Action, p. 13. According to the Examiner, Chasin discloses plasiticizers in oral compositions that include triethyl citrate and dibutyl stearate. The Examiner states that it would have been obvious to exchange dibutyl sebacate as taught by Chasin for the triethyl citrate taught by the combination of Oshlack B, Gordon, Oshlack C, Odds, and Grimm.

Claims 1-5 and 9 are non-obvious over the combination of Oshlack B, Gordon, Oshlack C, Odds, and Grimm for the reasons set forth in (2), above. Chasin teaches a single active compound in a controlled release dosage form. See, e.g., Chasin, col. 2, ll. 48-67. Ethylcellulose is disclosed as a coating ingredient, and not as a component of a matrix. Even more remote is any teaching of ethylcellulose in a substantially non-swellable diffusion matrix, and such a matrix that releases more than one active compound in an independent and invariate manner. Thus, Chasin does not provide the teaching missing from the combination of Oshlack B, Gordon, Oshlack C, Odds, and Grimm. Accordingly, this rejection should be withdrawn.

In sum, no combination of Miller, Oshlack, Oshlack B, and Gordon, discloses or suggests a plurality of formulations wherein two active agents and an inert pharmaceutical excipient may be altered in amount but maintain the same release profile. Declaration at 27-28. The secondary references (Oshlack C, Odds, Grimm, and Chasin) do not cure the deficiencies of Miller, Oshlack, Oshlack B, and Gordon. Thus, the rejections under 35 U.S.C. § 103(a) should be withdrawn.

Conclusion

This application is believed to be in condition for allowance. If any issues remain which may be addressed by an Examiner's amendment or a supplementary amendment, the Examiner is respectfully requested to contact the undersigned.

Respectfully submitted,

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